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(54) MEDICAMENTS POUR L'INDUCTION DE CELLULES T CYTOTOXIQUES
(54) MEDICAMENTS FOR INDUCING CYTOTOXIC T-CELLS

(57)

The invention relates to compounds containing an amino acid with the sequence X1-Y-X2-D-D-X3 or a nucleic acid coding this amino acid, X1 being at least one chosen amino acid, Y being tyrosine, X2 being an amino acid chosen from the following group: valine, isoleucine and leucine; D being aspartate and X3 being at least one other chosen amino acid, the following amino acids being excluded: TLVLQYVDDLLL and ILVLQYVDDLLL, T being threonine, V being valine, I being isoleucine, L being leucine and Q being glutamine. The invention also relates to medicaments for inducing cytotoxic T-cells, containing this class of compounds.

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(54) **MEDICAMENTS POUR L'INDUCTION DE CELLULES T CYTOTOXIQUES**

(54) **MEDICAMENTS FOR INDUCING CYTOTOXIC T-CELLS**

(57) L'invention concerne des composés comprenant un acide aminé ou un acide nucléique codant pour cet acide aminé, l'acide aminé ayant la séquence ci-après: X1-Y-X2-D-D-X3, où X1 désigne au moins un acide aminé quelconque, Y désigne la tyrosine, X2 désigne un acide aminé choisi dans le groupe comprenant la valine, l'isoleucine et la leucine, D désigne un aspartate, et X3 désigne au moins un autre acide aminé quelconque, à l'exception des séquences d'acides aminés suivantes: TLVLQYVDDLLL et ILVLQYVDDLLL, où T désigne la thréonine, V la valine, I l'isoleucine, L la leucine, et Q la glutamine. L'invention concerne également des médicaments pour l'induction de cellules T cytotoxiques renfermant cette classe de composés.

(57) The invention relates to compounds containing an amino acid with the sequence X1-Y-X2-D-D-X3 or a nucleic acid coding this amino acid, X1 being at least one chosen amino acid, Y being tyrosine, X2 being an amino acid chosen from the following group: valine, isoleucine and leucine; D being aspartate and X3 being at least one other chosen amino acid, the following amino acids being excluded: TLVLQYVDDLLL and ILVLQYVDDLLL, T being threonine, V being valine, I being isoleucine, L being leucine and Q being glutamine. The invention also relates to medicaments for inducing cytotoxic T-cells, containing this class of compounds.

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(54) Title: MEDICAMENTS FOR INDUCING CYTOTOXIC T–CELLS

(54) Bezeichnung: ARZNEIMITTEL ZUR INDUKTION ZYTOTOXISCHER T–ZELLEN

(57) Abstract

The invention relates to compounds containing an amino acid with the sequence X1–Y–X2–D–D–X3 or a nucleic acid coding this amino acid, X1 being at least one chosen amino acid, Y being tyrosine, X2 being an amino acid chosen from the following group: valine, isoleucine and leucine; D being aspartate and X3 being at least one other chosen amino acid, the following amino acids being excluded: TLVLQYVDDLLL and ILVLQYVDDLLL, T being threonine, V being valine, I being isoleucine, L being leucine and Q being glutamine. The invention also relates to medicaments for inducing cytotoxic T–cells, containing this class of compounds.

(57) Zusammenfassung

Die Erfindung betrifft Verbindungen, umfassend eine Aminosäure oder eine diese Aminosäure kodierende Nukleinsäure, wobei die Aminosäure die folgende Sequenz hat: X1–Y–X2–D–D–X3, wobei X1 = mindestens eine beliebige Aminosäure, Y = Tyrosin, X2 = eine aus der folgenden Gruppe ausgewählte Aminosäure: Valin, Isoleucin, Leucin, D = Aspartat, und X3 = mindestens eine weitere beliebige Aminosäure, wobei die folgenden Aminosäuresequenzen ausgenommen sind: TLVLQYVDDLLL und ILVLQYVDDLLL, wobei T = Threonin, V = Valin, I = Isoleucin, L = Leucin und Q = Glutamin bedeutet, sowie Arzneimittel zur Induktion zytotoxischer T–Zellen, die diese Klasse von Verbindungen enthalten.

Medicaments for Inducing Cytotoxic T cells

The invention relates to a compound or medicament for inducing cytotoxic T cells. The invention further relates to a vaccine against retroviruses such as HIV-1, HIV-2, HTLV-I, HTLV-II as well as against viruses such as hepatitis-B.

It is known from the prior art that by treatment with certain medicaments cytotoxic T cells (CTL) may be induced. Cytotoxic T cells eliminate inter alia virus infected cells specifically.

In the treatment of HIV infections, inhibitors of viral enzyme reverse transcriptase are employed. One important reverse transcriptase inhibitor used clinically is the medicament 3TC (which is (-)2'-deoxy-3'-thiacytidine or lamivudine). However, HIV may become resistant to this medicament by mutating methionine to isoleucine or valine at codon 194 of reverse transcriptase (PNAS 1993: 90: 5653-6). The same mutation also leads to resistance to other reverse transcriptase inhibitors such as 1592U89 (abacavir), zalcitabin (DDC), didanosin (DDI), and 2'deoxy-5-fluoro-3'thiacytidine (FTC). Other viruses also have reverse transcriptase or similar DNA polymerases that like HIV reverse transcriptase contain the sequence YMDD at the active catalytic center. The same mutation of methionine to valine in the YMDD sequence of hepatitis B DNA polymerase also induces resistance in the hepatitis B virus to 3TC, a medicament used to fight the hepatitis B virus.

From the later published application WO 98/23755, the following amino acid sequences are known for the treatment of multiple sclerosis:

TLVLQYVDDLLL and ILVLQYVDDLLL, whereby T = threonine, V = valine, I = isoleucine, L = leucine, and Q = glutamine.

The object of the invention is to make available a medicament that may be used to effectively block or positively affect the course of viral infections, particularly HIV or hepatitis B infections. This medicament should be suitable both for prevention of an infection, e.g. as a preventive vaccine, and for the therapy of an already established infection.

This object is fulfilled by the features of claim 1. Useful embodiments of the invention result from the features of claims 2 through 29.

According to the invention, a compound or medicament is provided for the induction of cytotoxic T cells containing or consisting of an amino acid or the nucleic acid encoding this amino acid, where such amino acid has the following sequence:

X1-Y-X2-D-D-X3,

wherein X1 = at least one of any amino acid,
Y = tyrosine,
X2 = one amino acid selected from the following group: valine, isoleucine, and leucine,
D = aspartate, and
X3 = at least one additional of any amino acid,
with the exception of the following amino acid sequences:
LRVEYLDDR, TLVLQYVDDLLL, and ILVLQYVDDLLL,
with T = threonine, V = valine, I = isoleucine, L = leucine, Q = glutamine, and R = arginine;

as well as a method for prevention or treatment of infections with viruses, preferably mutated HIV, HIV-1, HIV-2, HTLV-I, or HTLV-II viruses, or mutated hepatitis-B viruses, or a disease that responds to induction of cytotoxic T cells consisting of administering effective doses of the medicament comprising the amino acid with the following sequence:

X1-Y-X2-D-D-X3, wherein

X1 = at least one of any amino acid,
Y = tyrosine,
X2 = one amino acid selected from the following group: valine (V), isoleucine (I), and leucine (L),
D = aspartate, and
X3 = at least one additional of any amino acid,

or nucleic acid encoding such amino acid, and/or

the use for producing a medicament comprising the following amino acid:

X1-Y-X2-D-D-X3, wherein

X1 = at least one of any amino acid,
Y = tyrosine,
X2 = one amino acid selected from the following group: valine, isoleucine, and leucine,
D = aspartate, and
X3 = at least one additional of any amino acid,

or a nucleic acid encoding such amino acid sequence for production of a medicament for the prevention or treatment of a viral infection, preferably mutated HIV, HIV-1, HIV-2, HTLV-I, HTLV-II, or mutated hepatitis B infection, or a disease which responds to induction of cytotoxic T cells.

The medicament in this invention induces cytotoxic T cells which destroy cells particularly infected with mutated HIV viruses. Surprisingly, the sequences of this invention form T cell epitopes that are able to bind to HLA-A2 molecules and induce specific T cell receptors against themselves. Thus, it is possible to specifically target HIV mutants that arise in treatment with 3TC and abacavir.

According to one embodiment, the peptide consists of nine amino acids. X1 may consist of a sequence of four or five of any additional amino acids, X3 of one or two additional of any amino acids. Such an amino acid sequence is especially suited to immunize against mutant HIV viruses, but also against other viruses, e.g. mutated hepatitis B viruses.

For purposes of immunization, the amino acid sequence may be a component of a peptide or protein. The peptide or protein may be coupled to a lipopeptide or lipoprotein, preferably tripalmitoyl-S-glyceryl-cysteinyl-seryl-serine. Depending on the purpose, the peptide or protein may be contained within a liposome or ISCOM (immunostimulatory complex). The peptide or protein may however also be coupled to a viral protein which preferably is selected from the following group: HIV virus-like particles, HIV gag particles, or HBs antigens.

This peptide may preferably be present as a peptide-HLA complex in soluble form, e.g. as HLA-A2 tetramer. The above-mentioned complex may be bound to a liposome. The peptide may however also be part of a cell presenting an antigen, preferably a dendritic cell, macrophage, B cell, or CD4+ T cell. This may be achieved both by exogenic addition of the peptide to the cell and endogenic processing of proteins expressed in the cell.

According to the invention, this medicament may further contain cytokines such as interleukin-2 and/or GM-CSF, or polyvalent vaccines. It has proven especially beneficial to select the amino acid sequence from among the following sequences:

IVIYQYVDDL (SEQ ID NO:1), IVICQYVDDL (SEQ ID NO:2),
IVIYQYIDDL (SEQ ID NO:3), IVICQYIDDL (SEQ ID NO:4),
ITIYQYVDDL (SEQ ID NO:5), ITICQYVDDL (SEQ ID NO:6),
ITIYQYIDDL (SEQ ID NO:7), ITICQYIDDL (SEQ ID NO:8),

IIIYQYVDDL (SEQ ID NO:9), IIICQYVDDL (SEQ ID NO:10)
IIIYQYIDDL (SEQ ID NO:11), IIICQYIDDL (SEQ ID NO:12),
MVIYQYVDDL (SEQ ID NO:13), MVICQYVDDL (SEQ ID NO:14),
MVIYQYIDDL (SEQ ID NO:15), MVICQYIDDL (SEQ ID NO:16),
VIYQYVDDL (SEQ ID NO:17), VICQYVDDL (SEQ ID NO:18),
VIYQYIDDL (SEQ ID NO:19), VICQYIDDL (SEQ ID NO:20),
LIYQYVDDL (SEQ ID NO:21), LICQYVDDL (SEQ ID NO:22),
LIYQYIDDL (SEQ ID NO:23), LICQYIDDL (SEQ ID NO:24),
TILQYVDDILL (SEQ ID NO:25), TICQYVDDILL (SEQ ID NO:26),
ILQYVDDIL (SEQ ID NO:27), ILQYIDDIL (SEQ ID NO:28),
TIVQYVDDILL (SEQ ID NO:29), TIVQYIDDILL (SEQ ID NO:30),
IVQYIDDIL (SEQ ID NO:31), IVQYIDDIL (SEQ ID NO:32),
ILVQYVDDIL (SEQ ID NO:33), ILVQYIDDIL (SEQ ID NO:34),
IIIQYVDDIL (SEQ ID NO:35), IIIQYIDDIL (SEQ ID NO:36),
ILIQYVDDIL (SEQ ID NO:37), ILIQYIDDIL (SEQ ID NO:38),
VLYQYVDDL (SEQ ID NO:39), VLCQYVDDL (SEQ ID NO:40),
VLYQYIDDL (SEQ ID NO:41), VLCQYIDDL (SEQ ID NO:42),

where V = valine, I = isoleucine, L = leucine, M = methionine, C = cysteine, and Q = glutamine. The nucleic acid sequence may be a DNA or RNA sequence. It is possible for the nucleic acid sequence to be a component of a plasmid or viral vector, preferably of a recombinant vaccinia virus or recombinant adenovirus, or a retroviral vector. The nucleic acid sequence may also be a component of retroviral vectors or attenuated retroviruses. Furthermore, the nucleic acid may be a component of a bacterial vector, preferably a recombinant BCG or salmonella vector or inactivated virus, preferably HIV virus. According to the invention, the medicament may also be used in the ex vivo production of T cells or T cell receptors.

An additional object of the present invention is the use of a medicament according to the present invention for prevention or treatment of viral infection, preferably involving mutated HIV, HIV-1, HIV-2, HTLV-I, or HTLV-II viruses, or mutated hepatitis B viruses. The viruses may also be mutated viruses

resistant to (-)-2',3'-dideoxy-3'-thiacytidine [3TC (lamivudine)], (-)-(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purine-9-yl]-2-cyclopentene-1-methanol [abacavir], 2',3'-dideoxyinosine [didanosin], 2',3'-dideoxycytidine [zalcitabin], (-)-2'-deoxy-5-fluoro-3'-thiacytidine [FTC].

The efficacy of the medicament of this invention is, for example, explained using a graphic representation of experimental results. The following is shown here:

Fig. 1 recognition of CTL epitope VIYQYVDDL (SEQ ID NO:17) or VIYQYIDDL (SEQ ID NO:19) by CTL clone ETMV1 and non-recognition of CTL epitope VIYQYMDDL described above by the same clone,

Fig. 2 specific lysis of clone of ETMV1 during titration of peptides VIYQYVDDL (SEQ ID NO:17) and VIYQYIDDL (SEQ ID NO:19),

Fig. 3 recognition of peptide VIYQYVDDL (SEQ ID NO:17), and

Fig. 4 non-recognition of peptides VIYQYVDDL (SEQ ID NO:17) and VIYQYIDDL (SEQ ID NO:19) by CTL clone EB3, which recognizes the wild-type sequence VIYQYMDDL.

In Fig. 1, the peptides were pre-incubated at a concentration of 1 µg/ml for one hour with autologous EBV transformed B-cell lines labelled with ^{51}chromium. Four hours after addition of clone ETMV1 with an effector-target ratio of 15:1, the supernatant was harvested and the specific lysis was calculated based on the amount of chromium released. The p17-peptide KIRLRPGGK was used as control. As can be inferred from Fig. 1, only peptides IVIYQYVDDL (SEQ ID NO:1), VIYQYVDDL (SEQ ID NO:17), and VIYQYIDDL (SEQ ID NO:19) were recognized, which contain resistance mutations against

reverse transcriptase inhibitors. Wild-type peptide VIYQYMDDL was not recognized.

In order to achieve the results represented in Fig. 2, the peptides described therein were pre-incubated for one hour at concentrations as indicated with autologous EBV-transformed B-cell lines labelled with ^{51}chromium. Four hours after addition of clone ETMV1 with an effector-target ratio of 5:1, the supernatant was harvested and the specific lysis was calculated based on amounts of chromium released.

Fig. 3 indicates recognition of peptide VIYQYVDDL (SEQ ID NO:17) (=RT50 M/V). It is HLA-A2 restricted. The shown results were achieved by pre-incubating the peptide and control peptide for one hour at a concentration of 10 µg/ml with autologous EBV-transformed B-cell lines labelled with ^{51}chromium, HLA-A2-matched, or HLA-A2-negative allogenic B-cell lines. Four hours after addition of clone ETMV1 with an effector-target ratio of 5:1, the supernatant was harvested and the specific lysis was calculated based on amount of chromium released. Addition of antibodies to CD8 showed that lysis is HLA class-I restricted.

The table shown in Fig. 4 indicates recognition of variant peptides by clone EB3. For this purpose, peptides at indicated concentrations were pre-incubated for one hour with autologous EBV-transformed B-cell lines labelled with ^{51}chromium. Five hours after addition of clone EB3 with an effector-target ratio of 8:1 or 10:1, the supernatant was harvested and specific lysis was calculated based on amount of chromium released. This clone recognizes non-mutated wild-type sequence of HIV, but not the sequence of this invention. It is shown that the sequence of this invention is a new CTL epitope.

SEQUENCE LISTING

<110> Glaxo Group Ltd.
Harrer Dr., Thomas

<120> Medicaments for inducing cytotoxic T- cells

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<140> PCT/EP99/02249
<141> 1999-04-01

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<400> 34
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<210> 35
<211> 10
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<213> Artificial Sequence

<220>
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1 5 10

<210> 36

<211> 10
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<211> 10
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<220>
<223> Description of Artificial Sequence:Peptide

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1 5 10

<210> 38
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<220>
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<210> 39
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<220>
<223> Description of Artificial Sequence:Peptide

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1 5

<210> 40
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<210> 42
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<220>
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Val Leu Cys Gln Tyr Ile Asp Asp Leu
1 5

Claims

1. A compound containing or consisting of an amino acid or nucleic acid encoding said amino acid, wherein said amino acid has the following sequence:

X1-Y-X2-D-D-X3, wherein

X1 = at least one of any amino acid
Y = tyrosine
X2 = one amino acid selected from the following group: valine, isoleucine, and leucine
D = aspartate, and
X3 = at least one of any additional amino acid,
except for the following amino acid sequences:
LRVEYLDDR, TLVLQYVDDLLL, and ILVLQYVDDLLL, with
T = threonine, V = valine, I = isoleucine, L = leucine,
Q = glutamine, and R = arginine.

2. A compound according to claim 1, wherein said amino acid sequence consists of nine amino acids.

3. A compound according to any one of the preceding claims, wherein X1 is a sequence consisting of four or five amino acids.

4. A compound according to any one of the preceding claims, wherein X3 is a sequence consisting of one or two additional amino acids.

5. A compound according to any one of the preceding claims, wherein said amino acid sequence is a component of a peptide.

6. A compound according to any one of the preceding claims, wherein said amino acid sequence is a component of a protein.

7. A compound according to any one of the preceding claims, wherein said peptide or protein is coupled to a lipopeptide or lipoprotein, preferably to tripalmitoyl-S-glycerylcysteinyl-seryl-serine.

8. A compound according to any one of the preceding claims, wherein said peptide or protein is contained within a liposome or ISCOM.

9. A compound according to any one of the preceding claims, wherein said peptide or protein is coupled to a viral protein.

10. A compound according to any one of the preceding claims, wherein said peptide is selected from the following group: HIV virus-like particles, HIV gag-particles, or HBs antigens.

11. A compound according to any one of the preceding claims, wherein said peptide is present as a soluble peptide-HLA complex, preferably as a HLA-A2 tetramer.

12. A compound according to any one of the preceding claims, wherein said peptide is present as a soluble peptide-HLA complex bound to a liposome.

13. A compound according to any one of the preceding claims, wherein said peptide is a component of an antigen-presenting cell, preferably dendritic cell, macrophage, B cell or CD4+ T cell.

14. A compound according to any one of the preceding claims, wherein said amino acid sequence is selected from among the following amino acid sequences:

IVIYQYVDDL (SEQ ID NO:1), IVICQYVDDL (SEQ ID NO:2),
IVIYQYIDDL (SEQ ID NO:3), IVICQYIDDL (SEQ ID NO:4),
ITIYQYVDDL (SEQ ID NO:5), ITICQYVDDL (SEQ ID NO:6),
ITIYQYIDDL (SEQ ID NO:7), ITICQYIDDL (SEQ ID NO:8),
IIIYQYVDDL (SEQ ID NO:9), IIICQYVDDL (SEQ ID NO:10)
IIIYQYIDDL (SEQ ID NO:11), IIICQYIDDL (SEQ ID NO:12),
MVIYQYVDDL (SEQ ID NO:13), MVICQYVDDL (SEQ ID NO:14),
MVIYQYIDDL (SEQ ID NO:15), MVICQYIDDL (SEQ ID NO:16),
VIYQYVDDL (SEQ ID NO:17), VICQYVDDL (SEQ ID NO:18),
VIYQYIDDL (SEQ ID NO:19), VICQYIDDL (SEQ ID NO:20),
LIYQYVDDL (SEQ ID NO:21), LICQYVDDL (SEQ ID NO:22),
LIYQYIDDL (SEQ ID NO:23), LICQYIDDL (SEQ ID NO:24),
TILQYVDDILL (SEQ ID NO:25), TICQYVDDILL (SEQ ID NO:26),
ILQYVDDIL (SEQ ID NO:27), ILQYIDDIL (SEQ ID NO:28),
TIVQYVDDILL (SEQ ID NO:29), TIVQYIDDILL (SEQ ID NO:30),
IVQYIDDIL (SEQ ID NO:31), IVQYIDDIL (SEQ ID NO:32),
ILVQYVDDIL (SEQ ID NO:33), ILVQYIDDIL (SEQ ID NO:34),
IIIQYVDDIL (SEQ ID NO:35), IIIQYIDDIL (SEQ ID NO:36),
ILIQYVDDIL (SEQ ID NO:37), ILIQYIDDIL (SEQ ID NO:38),
VLYQYVDDL (SEQ ID NO:39), VLCQYVDDL (SEQ ID NO:40),
VLYQYIDDL (SEQ ID NO:41), VLCQYIDDL (SEQ ID NO:42),

where C = cysteine, D = aspartate, I = isoleucine, L = leucine, M = methionine, and Q = glutamine.

15. A compound according to any one of the preceding claims, wherein said nucleic acid sequence is a DNA or RNA sequence.

16. A compound according to any one of the preceding claims, wherein said nucleic acid sequence is a component of a plasmid or viral vector, preferably a recombinant vaccinia virus, adenovirus, or retroviral vector.

17. A compound according to any one of the preceding claims, wherein said nucleic acid sequence is a component of a bacterial vector, preferably of a recombinant BCG or salmonella vector.

18. A compound according to any one of the preceding claims, wherein said nucleic acid sequence is a component of an inactivated virus, preferably an inactivated HIV virus.

19. A medicament containing as active ingredient a compound according to any one of the preceding claims.

20. A medicament according to claim 19 in form of a vaccine.

21. A medicament according to claim 20 containing polyvalent vaccines.

22. A medicament according to any one of claims 19 through 21, wherein one or more cytokines are contained as adjuvant.

23. A medicament according to any one of claims 19 through 22, wherein interleukin-2 and/or GM-CSF are contained as adjuvant.

24. A method for the prevention or treatment of infections with viruses, preferably mutated HIV, HIV-1, HIV-2, HTLV-I, and HTLV-II viruses or mutated hepatitis B viruses or a disease responding to induction of cytotoxic T cells, consisting of administering to patient an effective dose of a medicament comprising a peptide of the following sequence:

X1-Y-X2-D-D-X3, wherein

X1 = at least one of any amino acid

Y = tyrosine,
X2 = one amino acid selected from the following group: valine (V), isoleucine (I), and leucine (L),
D = aspartate, and
X3 = at least one additional of any amino acid,

or a nucleic acid encoding said peptide.

25. A method according to claim 24, wherein said mutant viruses are resistant to reverse transcriptase inhibitors.

26. A method according to claim 24 or 25, wherein said mutant viruses are resistant to (-)-2',3'-dideoxy-3'-thiacytidine [=3TC (lamivudine)], (-)-(1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol [abacavir], 2',3'-dideoxyinosine [didanosin], 2',3'-dideoxycytidine [zalcitabin], (-)-2'-deoxy-5-fluoro-3'-thiacytidine [=FTC].

27. A use of the following amino acid sequence:

X1-Y-X2-D-D-X3, wherein

X1 = at least one of any amino acid
Y = tyrosine (T),
X2 = one amino acid selected from the following group: valine (V), isoleucine (I), and leucine (L),
D = aspartate, and
X3 = at least one of any additional amino acid,

or a nucleic acid encoding said peptide, for the preparation of a medicament for the prevention or treatment of infections with viruses, preferably mutated HIV, HIV-1, HIV-2, HTLV-I, and HTLV-II viruses or mutated hepatitis B viruses or a disease responding to induction of cytotoxic T cells.

28. A use according to claim 27, wherein said mutant viruses are resistant to reverse transcriptase inhibitors.

29. A use according to claim 27 or claim 28, wherein said mutant viruses are resistant to (-)-2',3'-dideoxy-3'-thiacytidine [=3TC (lamivudine)], (-)-(1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol [abacavir], 2',3'-dideoxyinosine [didanosin], 2',3'-dideoxycytidine [zalcitabin], (-)-2'-deoxy-5-fluoro-3'-thiacytidine [=FTC].

FIG.1

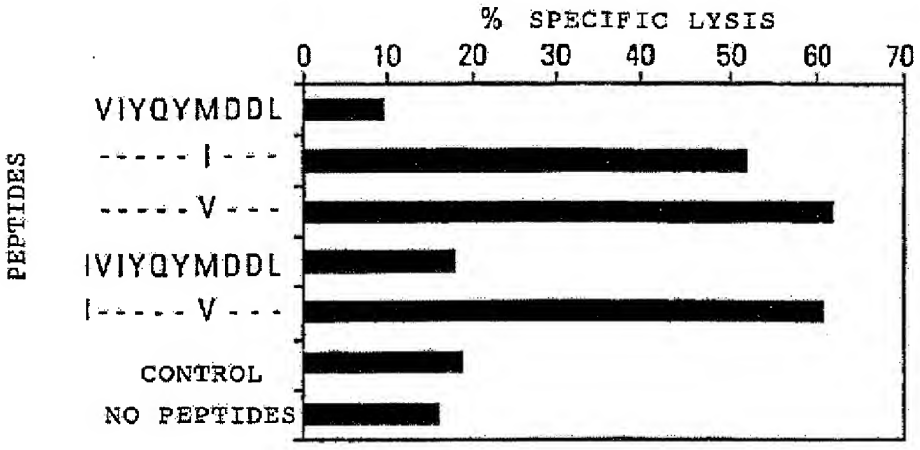
% SPECIFIC LYSIS
0
10
20
30
40
50
60
70
PEPTIDES
VIYQYMDDL
-----I---
-----V---
IVIYQYMDDL
I-----V---
CONTROL
NO PEPTIDES

FIG.2

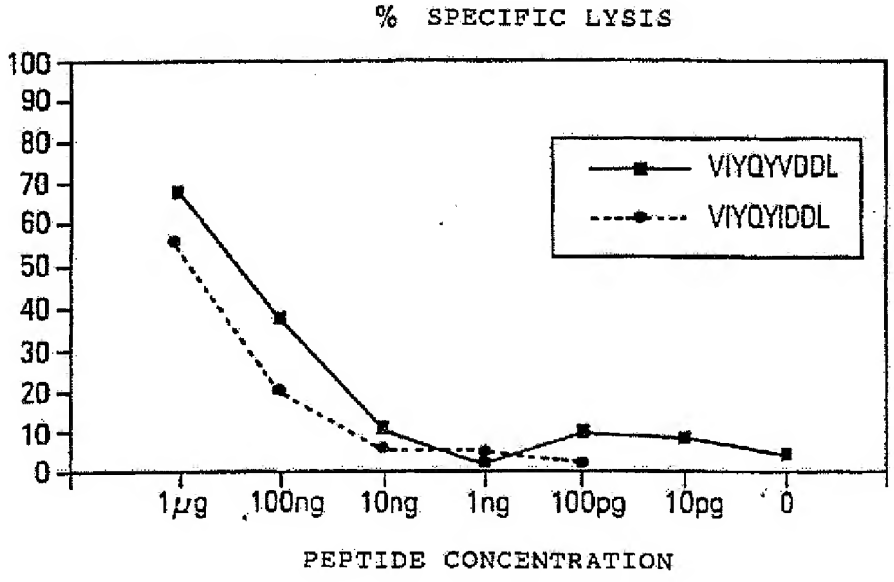
% SPECIFIC LYSIS
100
90
80
70
60
50
40
30
20
10
0
VIYQYVDDL
VIYQYIDDL
1µg
100ng
10ng
1ng
100pg
10pg
0
PEPTIDE CONCENTRATION

FIG.3

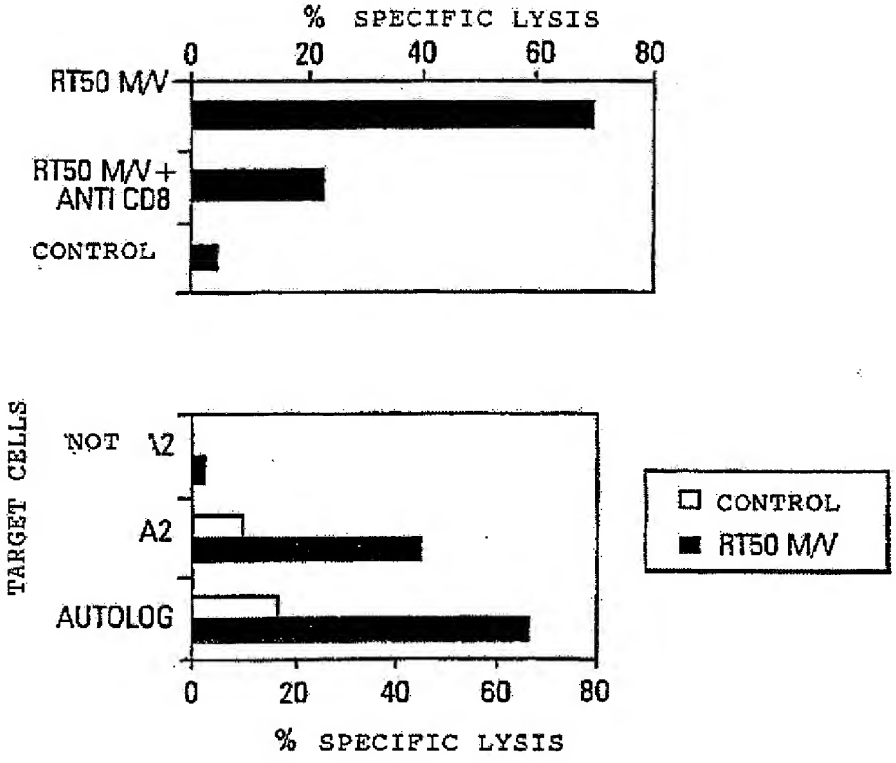

FIG.4

	% SPECIFIC LYSIS AT 100µmol	10µmol
VIYQYMDDL	64.9	57.3
--C------	25.8	2
-----V---	1.9	0